DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File 125562 for Anthrax Immune Globulin Intravenous (Human)

From: Randa Melhem, Ph.D., OCBQ/DMPQ/MRB II APPROVED

Through: Marion Michaelis, Branch Chief, OCBQ/DMPQ/MRB II APPROVED
John Eltermann, Jr., R.Ph., M.S., Director, DMPQ/OCBQ/CBER APPROVED m, Dec 31, 2014

Cc: Thomas Maruna, MSc, MLS(ASCP)^{CM},RPM, OBRR/RPMS
Robert Fisher, Ph.D., OBRR/DH/LH

Subject: **Review Memo (BLA):** [Cangene Corporation, License # 1201], Cangene is requesting approval for Anthrax Immune Globulin Intravenous (Human) supplied as a sterile frozen liquid in 50mL-vial presentation, and manufactured at Cangene facilities in Manitoba, Canada.

Action Due: March 25, 2015

RECOMMENDATIONS

I recommend approval of the BLA with the following inspectional issues to be considered on the next site inspection:

- [redacted]
- [redacted]
- [redacted]

SUMMARY

CBER received this electronic submission on 25 July 2014. Cangene Corporation (Cangene) doing business as (dba) Emergent BioSolutions submitted this BLA to provide information to support US market authorization of Anthrax Immune Globulin

Intravenous (Human) [AIGIV] presented as a sterile frozen liquid in single dose 50mL vials. Each vial contains ≥60 Units of activity as determined by the Toxin Neutralization Assay (TNA) with a target TNA potency of to allow for loss of potency during storage. In response to information requests Cangene provided clarification and additional information in amendments 125562/0/2 (received 16 Sep 2014) and 125562/0/9 received 03 Nov 2014 which are covered in this review memo.

Cangene received fast track designation (2006-12-21 FDA Approval Fast Track Designation); in addition, AIGIV was granted Orphan Drug designation (2008-07-29 FDA Approval Orphan Drug Designation); and this submission is accepted as a priority review BLA.

AIGIV contains no preservatives and is intended for single use by intravenous injection after thawing. The drug product is indicated for the treatment of adult and pediatric patients with toxemia associated with inhalational anthrax.

The efficacy of AIGIV was assessed in two animal models (rabbit and cynomolgus macaque) as clinical trials in a population exposed to anthrax are not feasible due to the small number of naturally occurring anthrax cases. In addition, AIGIV has been administered to 19 patients (as of July 2014) for the treatment of documented or suspected anthrax under the Centers for Disease Control and Prevention (CDC) sponsored Expanded Access Program (BB-IND 13026).

The process validation to support this BLA submission is "retrospective". No specific conformance lots for Human Anthrax Immune Globulin Drug Substance (AIG) or Drug Product (AIGIV) were manufactured as all AIG lots lots, one discarded) and AIGIV lots lots) were manufactured with the intent to release to the Strategic National Stockpile (SNS). All the manufactured lots met the requirements for the pre-Emergency Use Application (pre-EUA) designation, allowing distribution and administration by the CDC

AIG and AIGIV are manufactured using the validated hyperimmune platform process. Thus several validation/qualification reports of processes and equipment are applicable to other FDA approved products, and have been reviewed and approved in association with other licensed products.

Cangene implemented a

This information will be submitted for regulatory review when it is available.

Cangene implemented upgrades to the facility and equipment after the manufacture of the AIG and AIGIV lots. Cangene reported the qualification/validation of the equipment used 2005-2011, and also to the new equipment following the 2013 upgrades.

An inspection of the Cangene facilities in Manitoba, Canada is not required to complete the review of this BLA as documented in an Inspection Waiver memo. AIG (drug substance) and AIGIV (drug product) are manufactured using similar processes and

equipment/facilities as other FDA approved hyperimmune products manufactured by Cangene. In addition, The Facility was inspected by Team Bio in July 2014 and the inspection was classified as VAI (Voluntary Action indicated).

CATEGORICAL EXCLUSION FROM ENVIRONMENTAL ASSESSMENT

Cangene has submitted a request for a Categorical Exclusion to omit preparation of an Environmental Assessment, under 21 CFR Part 25.31(c) in amendment 125562/0/9.

Based on the information submitted and the nature of this product, I concluded that the sponsor's request for Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) is justified as this product is composed of naturally occurring substances and manufacturing of this product will not alter significantly the concentration and distribution of the natural substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

SUBMISSION REVIEW

Background/ Introduction

Anthrax Immune Globulin Intravenous (Human) [AIGIV] is prepared from Source Plasma obtained from selected healthy donors who have been immunized with anthrax vaccine adsorbed (AVA, BioThrax®). It is a clear or slightly opalescent colorless liquid essentially free of foreign particles that contains purified gamma globulin (IgG) antibodies to *Bacillus anthracis* and is stabilized with 10g% maltose and 0.03% (w/w) Polysorbate 80.

AIGIV is supplied in clear glass vials (50 mL) with bromobutyl rubber stoppers (20 mm), aluminum seals and plastic flip-top caps. Each vial contains ≥60 Units of activity as determined by the Toxin Neutralization Assay (TNA). The target fill volume is calculated based on a target TNA potency of

AIGIV is supplied as a frozen, sterile liquid formulation with no preservatives. It must be thawed and warmed prior to administration (no reconstitution or dilution is required) and is intended for single use by intravenous injection.

The following is a summary of the product information

Proprietary (Brand) Name of Drug Product	Anthrasil™
Common Name of Drug Product	Anthrax Immune Globulin Intravenous (Human) [AIGIV]
Common Name of Drug Substance	Anthrax Immune Globulin [AIG]
Manufacturer's Name	Cangene Corporation
Dosage Form	Sterile Liquid
Strength	Strength(s) ≥60 U/vial
Route of Administration	Intravenous infusion
Intravenous infusion Proposed Indication(s)	Treatment of adult and pediatric patients with toxemia associated with inhalational anthrax

Facilities and Equipment

Human Anthrax Immune Globulin Drug Substance (AIG) and Drug Product (AIGIV) are manufactured at Cangene facility in Manitoba, Canada. In-process testing is performed at contract testing labs as summarized below:

Site or Facility	Operations
Cangene Corporation 155 Innovation Drive Winnipeg, MB Canada R3T 5Y3 Registration (FEI) Number: 3003153579 Establishment DUNS number: 244844056	• Manufacture • Testing and release • Stability All operations/manufacturing steps and in-process/final product and stability testing except for testing contracted to other organizations listed below.
(b) (4)	General safety testing of Final Drug product
(b) (4)	Nucleic acid testing of (b) (4) and manufacturing pools
(b) (4)	Nucleic acid testing of (b) (4) and manufacturing pool
(b) (4)	(b) (4)
(b) (4)	(b) (4)
The following testing sites were previously used for (b) (4)	

Cangene also reported that all plasma collection, testing, storage and transportation establishments that supply plasma for manufacture of Anthrax Immune Globulin are approved for collection of plasma intended for further manufacturing. These sites are also routinely inspected by regulatory agencies.

Manufacturing Facility

Cangene Corporation's facility is located within a research and development park, and is used to manufacture human hyperimmune products as well as equine hyperimmune products according to similar manufacturing processes**.**

- Used for support activities such as warehousing, packaging, product storage, laboratories and office space.
-
- Utility generation systems including water for injection (WFI), purified water (PW), pure steam (PS) and compressed gases for the entire facility are located in this building.

  Note: Several documents from 2005 including media fill studies states that the operations/validations were performed in . Mr. Terry Kraynyk clarified that Cangene is the same Cangene manufacturing facility located at 155 Innovation Drive, Winnipeg, Canada; just the street names were changed.

To prevent contamination/cross contamination in the multi-product facility, Cangene provided, in addition to cleaning of equipment, brief descriptions of the facility, materials of construction, design, flows, personnel (access and gowning), room classifications and environmental monitoring (viables and non viables); the utilities, their monitoring and acceptance limits: water systems, the HVAC system and compressed gasses. They also stated that they manufacture on a campaign basis so that only one product is present in the manufacturing/filling areas at any time. In addition, line clearance/change control and

approval procedures for the manufacturing areas are performed between different lots/campaigns.

- All drug products and contaminated equipment have been removed, sealed, cleaned and/or stored from the previous operation.
- All dedicated equipment is adequately identified and in place.
- All equipment and instruments calibrations have not exceeded their expiry dates. A calibration report is attached to the Line Change Approval.
- The rooms are maintained under the appropriate pressure, as required.

> **Reviewer's comments**: Cangene confirmed in amendment 125562/0/9 that the manufacture of AIG and AIGIV uses the same facilities, equipment/rooms and procedures as other FDA approved human hyperimmune products all facilities/equipment/procedures have been submitted, reviewed and approved in association with other product submissions. Cangene provided the floor plan and flow diagrams for personnel, product, raw material, waste and packaging for Buildings [redacted]

They provided brief description of the utilities, their validation and routine monitoring as summarized below:

Water Systems

Cangene produces Purified Water (PW), Water for Injection (WFI) and Pure Steam (PS) using municipal water. [redacted] The initial validation and changes to the water system equipment and processes, as well as routine monitoring were previously reported and reviewed in association with other licensed hyperimmune product submissions.

Heating, Ventilation and Air Conditioning Systems (HVAC)

The HVAC systems at Cangene consist

- [redacted]

[redacted]. Following are the changes to the aseptic filling suite and the updates to the HVAC to accommodate the new areas (reviewed and approved in STN 103649/5654):

Compressed Gasses

[redacted]

- Nitrogen is supplied [redacted]

The following US licensed products are manufactured in [redacted] and filled into the Aseptic Filling Suite:

Product Name	Trade Name	Development Stage
Anthrax immune globulin (AIGIV)	Pending	Subject of this BLA STN 125562/0 (contract with US government for the SNS
Anti-D immune globulin	WinRho® SDF (liquid formulation)	Licensed in US Canada, and other countries
Anti-B immune globulin	HepaGam B® (liquid formulation)	Licensed in US, Canada and other countries
Vaccinia immune globulin	CNJ-016™	Licensed in US and Canada
Varicella Zoster Immune Globulin	VARIZIG®	Licensed in US and Canada
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Reviewer's comments: Cangene stated in STN 103649/5654 (approved April 2014) that they will no longer manufacture (b) (4) [redacted]		

The following US licensed products share the aseptic Filling Area, but are not manufactured in [redacted] Manufacturing Areas:

Product Name	Trade Name	Development Stage
Botulism Antitoxin eptavalent (A, B, C, D, E, F, G) – Equine), Sterile Liquid	eBAT NP-018	Licensed in US
Sphingomyelin Cholesterol	SCLI is a component of	Licensed in the US

Liposome Injection (SCLI)	vincristine sulfate liposome injection (Marqibo)	

Container Closure for AIG and AIGIV

Drug Substance

Cangene stated that in the commercial process, AIG will be routinely stored at [redacted] (validated hold time). They added that in cases where longer hold times are anticipated, the AIG bulk can be stored in [redacted] Cangene reported that a [redacted] construction was used for stability studies.

Descriptions of both containers are listed in the following Tables:

[redacted]

Reviewer's comments: The storage of the drug substance was discussed with Cangene during 18 Aug 2014 Telecon. They provided additional information in amendments 125562/0/2 and 125562/0/9 reviewed in **Q1&Q2** of the information Request section below.

Container Closure of the AIGIV Drug Product

AIGIV is filled in 50mL vials and closed with rubber stoppers described in the Table below. Cangene reported that container closure components have been used with other Cangene-manufactured products. They added that they have a reliable history with the suppliers; in addition, the functional quality and compatibility of the container closure with the hyperimmune products has been established.

Component	Description	Material	Supplier
Vial	50mL tubular vial	(b) (4)	(b) (4)
Stopper	20mm serum butyl rubber, (b) (4) ready to sterilize stopper	(b) (4) closure (gray-bromobutyl, (b) (4)	(b) (4)
Seal	20mm aluminum seal with plastic royal blue flip-off cap	Aluminum seal with polypropylene and resin cap	(b) (4)

Vials: Cangene stated that the vials are inspected and tested prior to release for filling, and the filled stoppered/capped vials are inspected as part of final release. The vials met *Containers – Glass* requirements and are compatible with aqueous protein products. Cangene provided a schematic diagram of the 50mL vial and listed the specifications and described the testing performed to demonstrate that the vials meet those specifications.

The vials are washed in the

Stoppers: The bromobutyl rubber stoppers meet the requirements for [redacted] The stoppers ar [redacted] The stoppers have a glass transition temperature of [redacted], as documented by the manufacturer. Thus they are suitable for use as closures for vials used for frozen preparations [redacted] of AIGIV. Cangene provided the schematic diagrams of the stoppers and the specifications presented below:

Seals with Flip-off Caps: Aluminum seals with plastic flip-off caps are used directly from the manufacturer's packaging. The seals are subjected to visual, dimensional and functional inspections per [redacted]. Cangene provided schematic diagram for the seals and the specifications presented below:

(b) (4)

Container Closure Testing

Cangene provided the following reports to determine the time it takes to freeze the AIGIV drug product for storage, and to determine the suitability of the container closure for storing frozen AIGIV.

- *VAL_PV_0102_rep_v1, Freezing Study for Liquid Product in 50cc Vials (approved 27 Jan 2009).* The study was conducted to determine (qualify) the time required for the AIGIV product in all vials to freeze.

  The study was performed using

  Reviewer's comments: Cangene clarified the temperature set point for the freezer is .

- *PQ#1125, Fill/Freeze/Thaw 20mm Serum Stoppers and 50cc Vials) (approved 16 Aug 2005).* This study was performed as a follow up to the

(b) (4)

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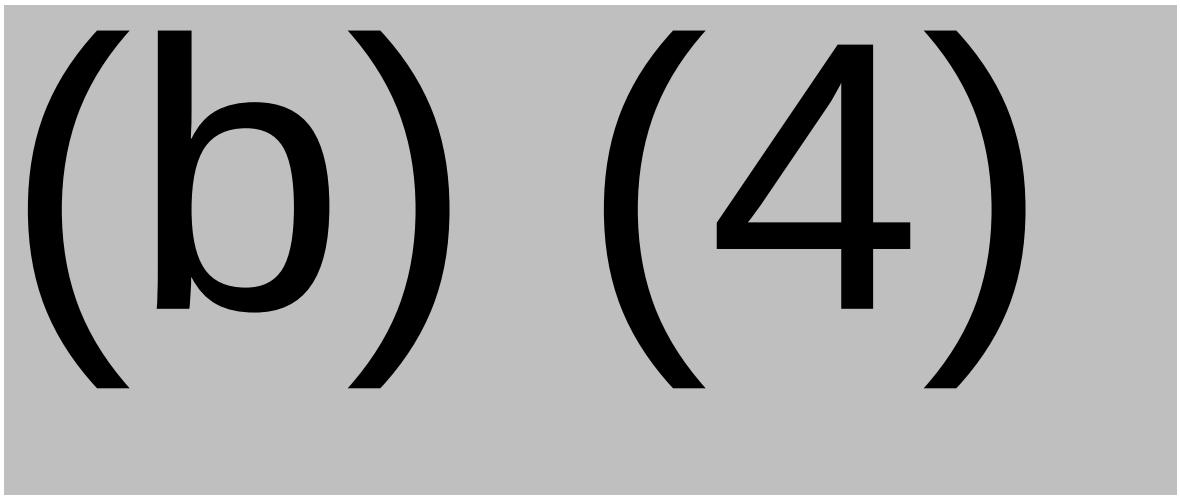
Reviewer's comments: This study demonstrates that 50mL vials can support a fill volume of ; however is does not demonstrate the suitability of the container closure as no container closure integrity testing was performed in study *PQ#1125*.

Cangene reported in amendment 125562/0/2 that they performed CCIT (with positive controls) using validation for PV_0151 described later and in the information Request section (**Q3-Q5**). No negative controls were used for the testing.

Reviewer's comments: AIGIV is a sterile parenteral product that is tested for sterility prior to release. It does not contain a preservative. Product sterility depends on prevention of microbial contamination during filling (aseptic processing) and during storage (container closure integrity). Cangene provided testing to demonstrate integrity of the container closure for AIGIV drug product; however the studies performed and the data provided did not assure of container closure integrity as summarized below:

- *PQ#1123, Closure integrity Tests 20mm Serum Stoppers and 50cc Vials), (approved 13 Oct 2005*). Cangene performed using the same lot of 50mL glass vials, 20mm neck diameter and the same lot of 20 mm bromobutyl stoppers.

2 pages determined to be not releasable: (b)(4)



Secondary Packaging

Vials of AIGIV are labeled and packaged in shelf cartons made from cardboard, which serve to protect the contents from light and the vials from breakage. Each shelf carton holds six 50 mL vials. Prior to shipping, shelf cartons are packaged into shipping cartons (24 shelf cartons/shipper).

Table 5 Description of the Secondary Packaging Components

Component	Description	Supplier	Identity of Materials
Shelf carton	Container for 50 mL vials	(b) (4)	Cardboard
Label	Label for shelf carton	(b) (4)	High Gloss with AT20 adhesive and Optically Brightened Pattern UV Varnish protective coating

Product Contact Equipment

Cangene stated that the manufacturing and filling product contact equipment used in the manufacture of AIG and AIGIV are also used (shared) for the manufacture of other human hyperimmune products. They stated that equipment is not shared between human and non-human Source Plasma hyperimmune products, or between hyperimmune and non-hyperimmune products.

> **Note**: In the BLA submission, Cangene refers to the equipment used for AIG and AIGIV as dedicated, which means that it is dedicated for the manufacture/filling of human hyperimmune products. The human hyperimmune products have similar composition except for the individual antibody of interest, which is a small proportion of the total IgG fraction.

Cangene listed in Tables 4-12 of eCTD *M3.2.A.1 Facilities and Equipment, Report 1*, the product contact equipment used for the different manufacturing operations and the method of cleaning: manual (M), or automated: clean in place (CIP) or cleaned out of place (COP) and whether the equipment is sanitized/sterilized: Steam in Place (SIP) or steam sterilized in an autoclave (A) as summarized below:

1 page determined to be not releasable: (b)(4)

Cleaning

Cangene reported that review of Material Safety Data Sheet (MSDS) for the cleaning and sanitizing agents determined that the agents were of low toxicity. They added that residual cleaning agents are detected using an [redacted] They stated that the [redacted] limits for the cleaning validations are set based on process capability to ensure consistent cleaning procedures. They added that validation studies showed that residual detergent levels are [redacted] below the worst-case toxicity level.

> **Reviewer's comments**: Cangene provided in amendment 125562/0/9 the acceptance criteria for the cleaning processes, and committed to re-evaluate the acceptance criteria for [redacted] as part of the 2015 equipment cleaning validation program taking into account the cleaning process capability. The information is reviewed in **Q6** of the Information Request section below.

[redacted]

12 pages determined to be not releasable: (b)(4)

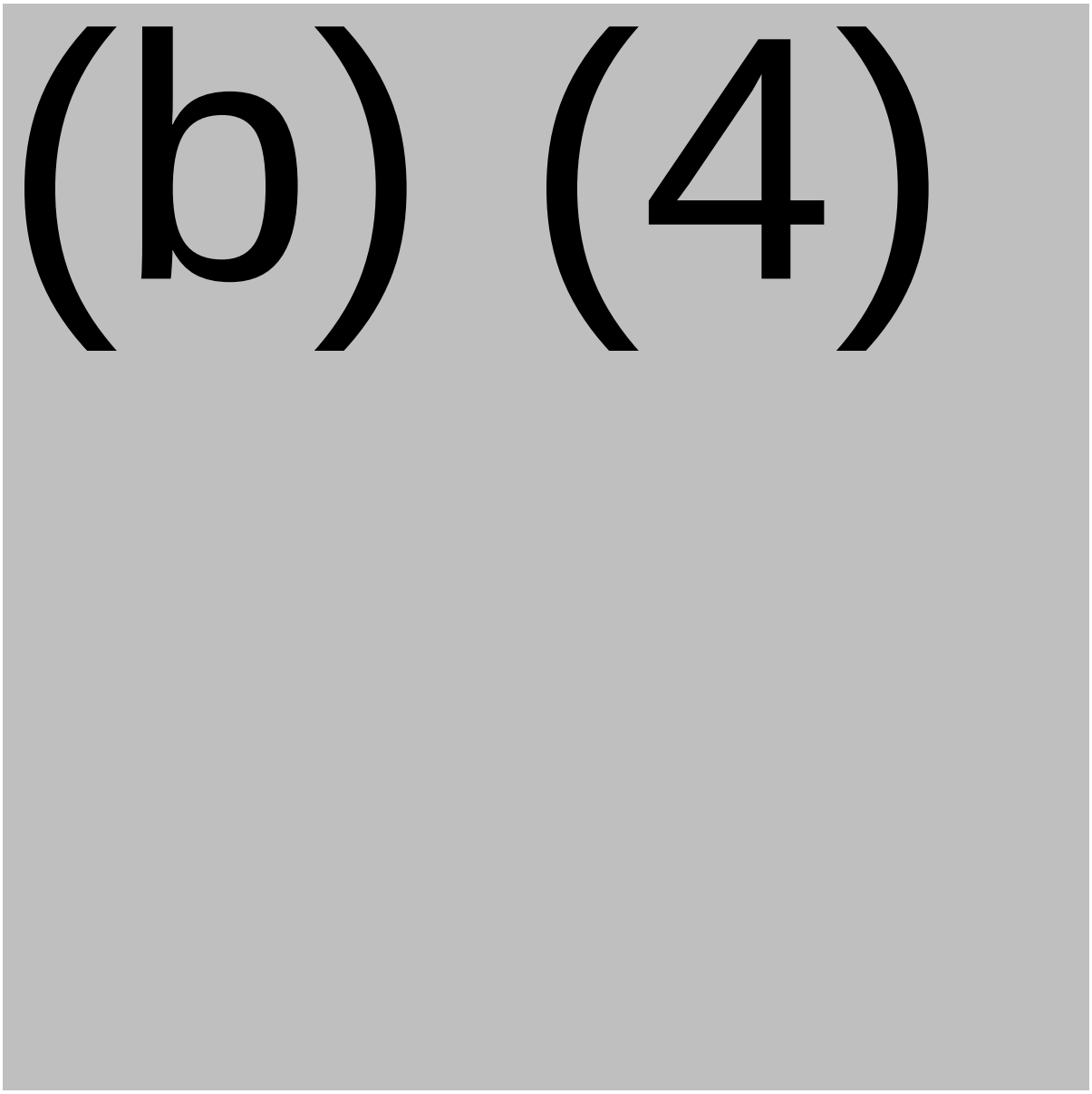
Manufacturing Process

Human Anthrax Immune Globulin Drug Product is manufactured and filled at Cangene facilities in Manitoba, Canada using the validated hyperimmune platform process. The manufacturing areas used for drug substance and drug product are shared with other human immune globulin (IgG) or contract manufacturing products. All products are manufactured on a campaign basis, so that only one product is present in the manufacturing or filling area at a time.

Human Anthrax Immune Globulin Drug Substance (AIG) is manufactured from donor plasma pools (Source Plasma) containing high titers of antibodies to *Bacillus anthracis*, the causative agent of anthrax.

The drug substance purification consists of an anion exchange chromatography step followed by viral reduction steps and The purified in-process IgG is concentrated, filtered and formulated, yielding the bulk drug substance. The AIG manufacturing steps are listed below:

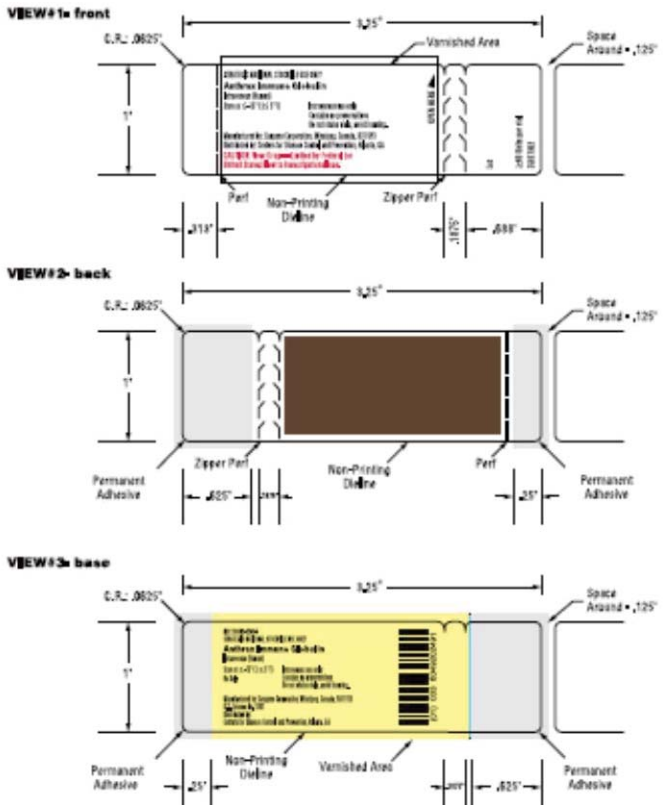
2 pages determined to be not releasable: (b)(4)



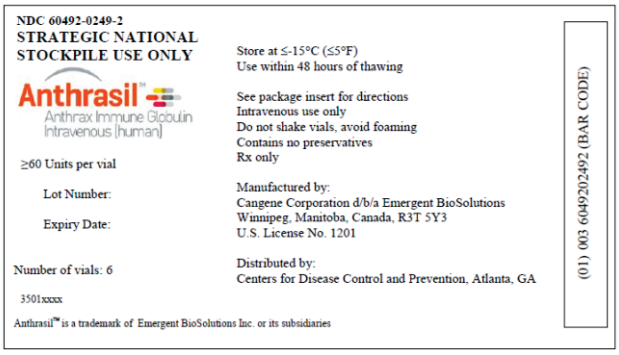
Cangene reported that the number of vials produced per lot to date has ranged from approximately , depending on the initial plasma titer, starting plasma pool scale, process recovery and number of bulk batches that are blended prior to filling.

Post-licensure Labeling Operation

AIGIV drug product vials manufactured under IND (11982) for the SNS were labeled with a single, two-layer vial label ("zipper label") so that the commercial label to be permanently affixed to the vial underneath the IND label in anticipation of required relabeling activities upon licensure. The lot number is printed on the portion of the label that is permanently affixed to the vial but is visible regardless of whether the IND or commercial text is exposed (zipper label shown below).



These vials will then be placed in a shelf carton bearing the commercial shelf carton label along with one package insert. The expiration date will be specified on the labels affixed to the commercial product shelf cartons as shown below:

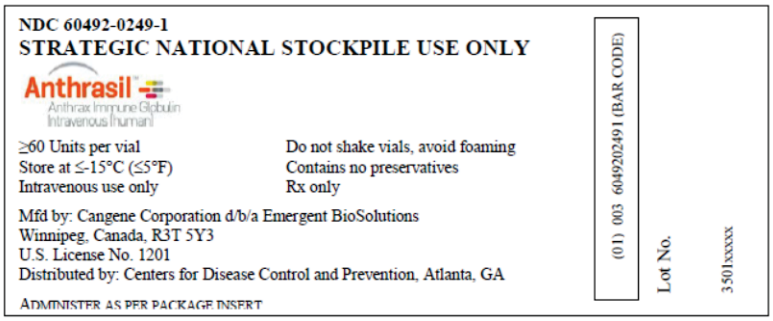


This process will be performed by Cangene personnel whether the product is held at Cangene facilities or at the SNS. For product stored at SNS, the labeling/packaging process will be performed at the SNS under CGMP controls, including Packaging Instructions, line approval and clearance, component-product reconciliation and quality assurance release.

Cangene stated that based on their discussions with the FDA and the agreements regarding the labeling/packaging post approval of IND products, they are requesting that

21 CFR 610.68 Exceptions or Alternatives to Labeling Requirements for Products Held by the Strategic National Stockpile be applied to AIGIV.

AIGIV product vials manufactured post BLA approval will be labeled with a single layer commercial vial label (shown below).


NDC 60492-0249-1
STRATEGIC NATIONAL STOCKPILE USE ONLY
Anthrasil
Anthrax Immune Globulin Intravenous (human)
≥60 Units per vial
Store at ≤-15°C (≤5°F)
Intravenous use only
Do not shake vials, avoid foaming
Contains no preservatives
Rx only
Mfd by: Cangene Corporation d/b/a Emergent BioSolutions
Winnipeg, Canada, R3T 5Y3
U.S. License No. 1201
Distributed by: Centers for Disease Control and Prevention, Atlanta, GA
ADMINISTER AS PER PACKAGE INSERT
(01) 003 604920249 1 (BAR CODE)
Lot No.
3501xxxxx

> **Reviewer's comments**: In response to information request, Cangene reported in amendment 125662/0/9 that SNS staff provides access to the product; Cangene is responsible for the over-labeling and removal of zipper labels as well as all QA oversight. The employees involved with performing the labeling tasks at the SNS are qualified Packaging personnel. The approval for these processes is governed by Cangene QA personnel at the SNS sites with final QA management approval of the documents at the Cangene Winnipeg site.

Process Validation

Cangene stated that specific conformance lots were not produced to support the licensure of Anthrax Immune Globulin Intravenous (Human), as AIG lots (b) (4), one discarded) and AIGIV lots (b) (4) were manufactured under IND with the intent to release to the Strategic National Stockpile. AIG and AIGIV lots were manufactured between 2005 - 2011. Cangene have made changes to equipment of rooms to update the filling suite in 2013. They provided in this submission validation reports for equipment prior to 2013 and post 2013 updates. In this memo I covered the following studies.

Equipment /Process	Report #	Report Title (Date approved)
Mixing	PV.HYP.02.13	Validation for the Mixing Parameters in the (b) (4) (approved 01 May 2003)
Media Fills	PQ 2017	50cc Vial Media Fills, Lot#(b) (4), 2450502, 2450503 (b) (4) (approved 13 Oct 2005)
Vial Washing (Reviewed under STN	PQ 2032	50 mL Vial Wash Coverage Challenge (b) (4) Vial Washer)

103649/5654)	PQ_2524_v1	(b) (4) Vial Washer Tag(b) (4): Wash Coverage and Non-Visible Particulate Testing Following Modification to the Vial Washer and Wash Cycle – 2013 Summer Shutdown
Depyrogenation (Reviewed under STN 103649/5654)	PQ 2014	(b) (4) Depyrogenation Oven 50 mL Vial Load Configuration
	PQ_2476_v2	(b) (4) Depyrogenation Oven
Sterilization (Reviewed under STN 103649/5654)	PQ 0344	Sterilization of(b) (4) 20 mm Non-lyophilization Stoppers
	PQ 2005	Sterilization of 50 mL Filling Equipment (Load Configuration) Autoclave(b) (4)
	PQ_2511_v1	(b) (4) Autoclave (b) (4): Sterilization of Serum Stoppers
	PQ_2475_v2	(b) (4) Autoclave (b) (4) Sterilization of Filling Equipment
Filling Machine	IQ/OQ 0258-5	Filling Machine - (b) (4) 50 mL Changeover
Capping Machine	IQ/OQ 0352-3	(b) (4) Capping Machine – 50 mL Change Parts
Labeling	IQ/OQ 0281-5	(b) (4) Labeller 50 mL Vial Size
	PQ_2468_v1	Fully Automatic Labeling Machine for Self-Adhesive Labels; (b) (4)
Shipping	VAL_PQ_2244_v1	Insulated Custom Shipping Crate
	PQ_2302_v1	≤-15°C Product Shipping using Insulated Custom Crate
	VAL_PQ_2260_v1	(b) (4) -15°C Shipments
	PQ_2286_v1	(b) (4) Shipping Qualification; ≤-15°C Shipment

Mixing Studies

PV.HYP.02.13, Validation for the Mixing Parameters For the [redacted] *Cangene's Hyperimmune Process (approved 01 May 2003)*

[redacted]

(b) (4)

[redacted]

[redacted]

)

Reviewer's comments: Clarification and additional information about mixing speed and mixing tanks was provided in amendment 125562/0/9 and reviewed in **Q13&Q14** of the information Request Section below.

Sterile Filtration

[redacted]

(similar formulation to AIGIV), which were processed, formulated and filtered in accordance to routine manufacturing conditions.

Reviewer's comments: Cangene clarified in amendment 125562/0/9 that the filter validations, documented under PV_0092 were performed by [redacted] per the schedule listed in the Table below:

[redacted]

They added that the validation studies were previously submitted and approved by FDA in BLA STN 125109/0 (VIGIV) approved 03 May 2005, and STN 125430/27 (VARIZIG, liquid formulation) approved 29 Sep 2014. They added that Validation Guide for [redacted] was submitted under STN 125109/53 (VIGIV) approved13 Dec 2007.

The filter validations were executed with liquid formulated drug substances that were processed, formulated and filtered in accordance to routine manufacturing conditions using the Cangene hyperimmune platform process. The test drug substances are comparable to the current specifications and target values for the AIG drug substance as summarized in the following Table:

[redacted]

Reviewer's comments: Cangene did not provide validation of sterile filtration using AIG or AIGIV. They validated the sterile filtration using other licensed hyperimmune products with comparable specifications (protein concentration, pH, density, maltose, and Polysorbate 80 concentration). While this is not the ideal validation strategy for sterile filtration of the AIG/AIGIV, it is acceptable as the AIG and AIGIV have comparable product specifications (except for the antibody specificity) to the other products used for the validation of sterile filtration process.

Aseptic Process Simulations (APS)

Cangene performs routine simulations of the aseptic process using microbiological media [redacted] instead of drug substance). The APS includes transfer of the bulk product into the filling suite through a sterilizing grade filter, followed by the dispensing into vials, stoppering, sealing and capping of the filled vials. The following activities are also performed as part of the media simulations: washing and depyrogenation of vials, sterilization of stoppers and sterilization of the filling tank/equipment.

Cangene provided the initial media simulation studies *PQ2017, 50cc Vial Media Fill PQ 2017* [redacted] *(approved 13 Oct 2005)* performed in October 2005 at the [redacted], to qualify the aseptic processing/filling using the container closure used for AIGIV. They stated that the media fills were conducted with maximum number of personnel and process manipulations [redacted]

Cangene reported that microbial environmental and personnel monitoring were performed during the media fills and the morphology of the bacteria were identified (they did not provide the data in the report).

Cangene reported that [redacted] different vial sizes [redacted] and [redacted] different stopper types [redacted] were used during the manufacturing of AIGIV lots from 2005 to 2011. They added that [redacted] media fills have been executed using the aseptic filling line at their facility, from April 1999 through August 2014. Only one failure was reported, the cause was identified followed by re-validation. I list below the media fills performed using 50mL vials.

1 page determined to be not releasable: (b)(4)

(b) (4)

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Shipping Qualification/Validation

Cangene stated that they have several qualified commercial shipping solutions and shipping containers that can accommodate the shipping of different load sizes at by air and ground transportation. The process involves the use of appropriately qualified containers (suitable for the shipment size), and the use of calibrated data loggers for temperature monitoring. Small loads will be shipped using single use containers, while larger loads will shipped using re-usable containers, with instructions to the end-user for return of the containers.

Ground transportation is currently used for shipping frozen drug products (AIGIV and Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G) – (Equine) [eBAT NP-018], a second biodefence product manufactured by Cangene) from Cangene Winnipeg facility to the United States (SNS). Cangene has also shipped AIGIV by air to international destinations.

Ground Shipment

Cangene reported that they currently use trucks for shipment of AIGIV, with product stored within temperature pre-conditioned crates. The crates are manufactured by for use during shipment of frozen products.

The product is transferred from the storage freezer to the crates which are then loaded on the refrigerated trucks. The crates have been qualified to maintain temperature of the product during the transfer and in case of malfunction of the on the truck. In addition the crates minimize temperature fluctuations of the product during transport, .

Cangene provided PQ report *VAL-PQ_2244_rep_v1, Insulated Shipping Custom Crate (approved 01 Sep 2009)* which provides the protocol and data for the qualification of the crates to maintain temperature of the shipped 50mL when stored at ambient temperature [redacted] and elevated Temperature [redacted]

Cangene provided a description of the custom [redacted] crates: [redacted]

Cangene provided the results of the [redacted] trials which show that the crates can maintain temperature for a certain period of time; however, there were large differences between the locations of the dataloggers in the loads and inconsistent correlation between air and vial at the same location as shown in the following Table:

(b) (4)

When stored at

When stored at an

Cangene concluded that the validation demonstrates that the use of the

Cangene also provided PQ *report PQ_2302_rep_v1, ≤-15°C Product Shipping using Insulated Custom Crate (approved 15 Dec 2010)* which documented the use of the custom crates and transport trucks trucks with validated temperature of under actual shipment conditions, over winter and spring temperature conditions for Both the Anthrax Immunoglobulin (AIGIV) and the Botulinum immunoglobulin (BAT).

Cangene reported that air temperature was monitored throughout the transport/shipping procedure by placing data loggers in the load which confirmed that the temperature inside the shipping cartons remained at ≤ -15°C.

(b) (4)

Reviewer's comments: The qualification of Ground Shipping was discussed with Cangene during 18 Aug 2014 telecon and additional information was provided in amendments 125562/0/2 and 125562/0/9 and reviewed in **Q17&Q18** of the Information Request section below.

Qualifications for Air Shipments

Cangene stated that the frozen AIGIV and BAT are shipped frozen to other countries using validated
Cangene provided *VAL_PQ_2260_rep_1,* *at ≤ -15°C (approved 23 Jul 2010)*. The study was performed by the supplier to simulate the air shipment temperature cycle (max and min vial loads) to an overseas destination from Cangene Corporation, under worst case conditions: summer conditions (refer to summer profile below) and increased hold times

(b) (4)

(b) (4) simulated shipment trials were executed:

- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

Cangene reported that the protocol generated by [redacted] was reviewed and approved by the Validation and Supply Chain departments of Cangene; however it was not approved by Cangene QA which is a deviation from *SOP 11.001.0001*. They clarified that the internal report generated by Cangene's Validation department is reviewed by the QA department.

Cangene reported the results for the different dataloggers in Tables 5:1 to 5:3 of the report which show that the temperature was maintained between [redacted] for the duration of the simulated process [redacted] for max load and [redacted] for min loads) as summarized in the following Table:

Parameter	Acceptance criteria	Results	Pass/Fail
Temperature	(b) (4) [redacted] .	(b) (4) [redacted]	Pass
		(b) (4) [redacted]	Pass
		(b) (4) [redacted]	Pass

Cangene concluded that the study demonstrated that the [redacted] can maintain the temperature under worst conditions (time and temperature).

In addition to qualifying the [redacted] (by the supplier), Cangene performed actual air shipping using the [redacted] filled with an approximate minimum load of product. The shipment took place in summer to desert climate. They provided *PQ_2286_rep_v1,* [redacted] *Shipping Qualification ≤15°C (approved 27 Aug 2010)*.

1 page determined to be not releasable: (b)(4)

(b) (4)

Cangene reported that the results met the acceptance criteria as shown in the Table below and concluded that the shipping is validated for load configurations at or between the minimum and maximum tested loads of , comparable to 50mL vials or equivalent.

They stated that the packaging of the product using the still allowed for a temperature spike. They added that if the temperature spikes during initial loading remain an issue they will have to .

Parameter	Acceptance Criteria		Pass/Fail
Product Temperature	(b) (4)	(b) (4)	Pass
		(b) (4)	Pass

Reviewer's comments: The qualification of Air Shipping was discussed with Cangene during 18 Aug 2014 telecon and additional inf1ormation was provided in amendments 125562/0/2 and 125562/0/9 and reviewed in **Q19&Q20** of the Information Request section below.

INFORMATION REQUEST

Additional information was requested during an 18 August, 2014 telecon and in two information requests dated 04 September 2014 and 14 October 2014. Cangene submitted their responses in amendments 125562/0/2 and 125562/0/9.

CBER comments are in ***bold italics***, followed by Cangene responses in plain lettering.

The information provided by Cangene was accepted because the product was manufactured according to the hyperimmune manufacturing process which was approved for other products. In addition the product was manufactured in 2005-2011 based on GMPs at the time.

Container Closure

- Drug substance

1. ***You stated that in the commercial process, AIG will be routinely stored at [redacted] for a maximum of [redacted] (validated hold time). You then added that in cases where longer hold time is anticipated the AIG bulk can be filled in [redacted]***

   Will both containers - [redacted] be used for the storage of the bulk? If you are requesting approval for storage of the [redacted] bulk in the [redacted] – please provide the validated procedure for filling [redacted], the validated storage time and the validated procedure for [redacted] to the mixing tank in preparation for mixing, sterile filtration and filling.

   [redacted].

[redacted].

[redacted].

[redacted]

Reviewer's comments: Additional clarification about the implemented CAPAs was requested and Cangene submitted their response in amendment 125562/0/9 reviewed in **Q2** below.

2. ***Have you performed a prospective study using a surrogate to simulate the storage of the drug substance to determine if the CAPAs implemented worked. Please justify your response***.

Cangene reported that they have not performed a prospective study, nor do they plan to execute one to determine if the CAPAs implemented have worked.

[redacted]

- Drug Product

3. You provided several studies to demonstrate integrity of the container closure of the frozen vials; however the procedures used, and the results obtained do not assure container closure integrity. Please provide additional information, justifications and/or propose to perform additional CCIT to demonstrate integrity of the container closure throughout the shelf life of the product)

Cangene reported that they submitted the CCIT validation documented under *PQ 1123* to provide historical information on the selected container closure system. They stated that they recognize that the initial CCIT validations, provided as supporting studies, do not meet the current expectations of the FDA. They added that they have implemented improvements with respect to the use of positive controls in the current validations (i.e. *PV_0151* and *PV_0275*) described below.

4. Please justify why you consider the study PV_0275 – two trials with one positive control of each size [redacted] and [redacted] test vials is sufficient to demonstrate validity of the method. Please describe the negative control used.

Cangene explained that preparation, vacuum conditions and selection of the defect size for the positive controls were initially qualified under the report *EV 0134*, which was [redacted]

(b) (4)

Reviewer's comment: The use of positive control would not add value as it can be positive or negative. Using positive controls with would give more assurance that the testing is performed properly.

5. Please clarify if you implemented the use of CCIT at expiration to demonstrate integrity through-out shelf life? Please justify your response.

Cangene reported that the key study supporting the CCIT over shelf-life is the on-going PV 0151 validation using

In addition, Cangene provided in amendment 125562/0/2 *VAL_PV 0151_pro vl_AD02, Closure Integrity Testing for Frozen Product Vials; Year Study (20mm Serum Stoppers and 50mL Vials) (approved 22 Aug 2014).*

They .

Cleaning Validation

6. Please provide the acceptance criteria for the following metrics:

Cangene provided the acceptance criteria as summarized in the following Table and committed to re-valuate the acceptance criteria, to include process capability, during the 2015 equipment cleaning validation program.

Reviewer's comments: The acceptance criteria are high for both . However, as the product was manufactured in accordance with other licensed hyperimmune products processes, using the same equipment and cleaning validations, that have been reviewed and approved by CBER, I will not ask additional questions regarding this issue.

(b) (4)

7. Please provide PV_0234 protocol and report (data).

Cangene provided the following protocol and addenda as well as interim data to support the validation of the new

- Protocol: *PV 0234 pro v1, Validation of the*

:

1 page determined to be not releasable: (b)(4)

(b) (4)

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8. ***You stated that PV_0256_v2 provides the results and protocol for a confirmatory run as the process has already been validated. Please clarify if the cleaning validation of the [redacted] were submitted, reviewed and approved by FDA; please provide the STN #, and approval date. Please provide the results of the most recent revalidation study.***

Cangene reported that PV_0256 report was previously submitted and approved (HepGamB, WinRho SDF and VARZIG-Liquid). They provided the results which met the acceptance criteria as shown in the following Table:

[redacted]

Reviewer's comments: The acceptance criterion for [redacted] is currently set at [redacted] (and not [redacted] as written in the Table). The acceptance criteria for all parameters are set much higher than the data collected (and thus the process capability) which could mask a problem with the cleaning. This issue should be discussed with Cangene during the next surveillance inspection.

(b) (4) **Systems**

9. Please provide PV_0258 protocol and report (data).

[redacted]

- [redacted]
- [redacted]

[redacted]

Capping Machine

10. Has the qualification of the capper including the displaced stopper detection system and RSF been submitted and reviewed by FDA in association with other submissions? Please provide the STN number(s) and approval date(s). Otherwise provide the qualification report(s).

Cangene stated in amendment 125562/0/9 that qualification of the capper including the displaced stopper detection system and residual seal force (RSF) was discussed within the VARIZIG Liquid submission (BL 1254530/27; approved Sep 29, 2014). They added that the documents were not submitted to FDA with the submission, but they updated eCTD section 3.2.P.3.5 to include the machinability using [redacted] vials, and the IOQ and PQ reports for qualification the raised stopper sensor.

The [redacted] The capping machine was initially validated under IQ/OQ 0352;

the raised stopper detector was initially validated under VAL_IQ/OQ_0352_ADD001 and VAL_PQ_0352_ADD001.

The sensor

The IQ/OQ included document verification,

The PQ was performed .

Cangene also presented PQ 2364 rep v1,

However, the AIGIV container closure is a 50mL vials and that was not addressed in the response.

Labeler for the 50 mL Vial Size

11. Please clarify whether the qualification and requalification of labeler has been submitted and reviewed by the Agency. Please list the STN number and approval date. Otherwise provide the qualification report(s).

Cangene stated the qualification and requalification reports for the labeler have not been submitted to any of the other licensed hyperimmune products manufactured by Cangene Corporation and they provided report *EQ 0058 _rep_v1, Fully Automatic Labeling Machine for Self-Adhesive Labels, (approved 14 Mar 2012)*. The report provides the qualification of the equipment using , but it does not describe the labeling of the 50mL vials.

> **Reviewer's comments**: This labeler would be used for labeling the new lots of AIGIV, but does not apply to the current lots. The labeling machine and visual system should be verified during the next surveillance inspection.

12. ***In the IQ/OQ (EQ_0058) you reported that the maximum acceptable reject rate is [redacted] of the total number of vials labeled per vial size. However, in the PQ_2468 report, the maximum allowed reject rate is [redacted]. Please clarify***.

Cangene explained that the [redacted] reject rate in EQ_0058 is a protocol specification that was set tighter than the manufacturing limit [redacted] to ensure that the setup and operation of the labeler and vision system would be able to consistently operate inside the manufacturing limit; however this [redacted] reject rate) is not a requirement in SOP *4.000.0001 Packaging of Product*. They added that the maximum reject rate during the labeler qualification was [redacted]

Process Validation – Mixing Studies

13. In PV.HYP.02.13 you state that the set mixing time is [redacted] however you reported that the set mixing time is [redacted]. Please clarify when this was changed and the reasons for the change.

Cangene explained that the validation of mixing studies included testing different batches with varying times and speeds [redacted]. The study concluded that mixing should be performed for [redacted] Cangene reported that the mixing parameters implemented in the Manufacturing Batch Record were: mixing speed of [redacted] which are within the validated parameters tested.

14. Please provide the schedule for requalification of the mixing tanks and the most recent data to support that the mixing vessels are functioning as intended.

Cangene reported that mixing of the product intermediates are continuously verified by confirmation of adequate mixing speed and time and the in-process testing conducted with each batch. Compliant results indicate that the mixing vessels are functioning as intended. In addition, they have preventive maintenance programs for the mixing tanks [redacted]

Aseptic Media Simulations (APS)

15. ***You provided in this submission the initial media fill simulations in 2005. You have provided in STN 103649/5654 media fill simulations following the upgrade of the facility (which was not provided in this BLA submission). It appears that the media simulations were run at different speeds in the initial (2005) and the recent (2013) media fills. Please provide the parameters for the current filling operations***.

Cangene stated that they updated eCTD section 3.2.P.3.5 to include the recent media fills. They added that they run [redacted]

16. You reported that the media fills are performed [redacted] however during the recent biennial inspection (July 2014), the inspector noted that the line speed for the media fills was not documented and thus speed could not be verified. Please explain.

Cangene explained that they determined the speed of the line based on the [redacted]. However following the FDA observation, they updated the protocol and the batch record to record the actual line speeds (instrument setting).

Ground Shipping

17. You reported that you ship to the US by ground transportation and to other countries by air. You provided simulated and actual shipping for both. The reports provided do not provide the temperature mapping of the containers to demonstrate that dataloggers placed in the loads during shipping record temperature data representative of the product temperature throughout the loads. Please provide additional information and justification to support that the shipping processes consistently maintain the product temperature between [redacted] under worst case conditions.

Cangene reported that they perform the storage and shipping of the AIGIV drug product based on [redacted] licensed hyperimmune drug products. The number of temperature probes used depends on the size of the area to be monitored.

They added that for the ground shipping of AIGIV, they use [redacted] trucks with a set temperature of [redacted] and they provided the validation for the temperature mapping of the trucks. I reviewed the temperature validation for the trucks, and it is acceptable with a set temperature of [redacted] which is outside the -15°C temperature limit for AIGIV.

Cangene clarified in amendment 125562/0/9 (response to 14 Oct 2014 information request) that the qualification of the [redacted] demonstrated a tolerance of [redacted] Thus to ensure transport of the AIGIV product remains within the label claim of ≤-15°C, the trucks used for transport are set at [redacted] In addition they also use the custom crates for protection against temperature fluctuation.

18. You provided reports of actual shipping during winter (Jan2010) and spring (Apr2010) for AIGIV and BAT using [redacted] transport trucks [redacted] trucks with validated temperature of [redacted] However, if you plan to ship in the summer, you need to provide validation during summer shipping. Please provide data.

Cangene provided summer shipping data (summarized below) and stated that all data loggers obtained from the loaded crates met the acceptance criterion, confirming that the temperature requirements were maintained during the approximate [redacted] shipping process. They added that the data confirms that the crates, used in conjunction with a [redacted] truck having a temperature set point of [redacted], can maintain the product at ≤-15ºC.

[redacted]

Air Shipping

19. You stated that the frozen AIGIV and BAT are shipped frozen to other countries using validated [redacted] shipping container [redacted] and provided VAL_PQ_2260_rep_1, [redacted] at ≤ -15°C (approved 23 Jul 2010). Review of the graphs shows that the recorded temperature fluctuates with the simulated temperature cycle – thus if the temperature is below zero, there is a possibility that the temperature (max load, Top corner) may drop below [redacted] thus causing stopper integrity issues. Please provide a risk assessment and data to assure that the temperature of the shipment will not drop below [redacted]

Cangene stated that the pack-out procedures were designed specifically for Cangene to maintain temperatures between -15 and [redacted], and were verified to be adequate and consistent during the execution of (VAL_PQ_2244) under the worst-case conditions. The lowest temperature recorded for the shipping challenge qualification was with the maximum load at a temperature of [redacted], which is still [redacted] above the minimum limit of [redacted]. They added during the actual shipping to [redacted], the minimum temperature was -[redacted].

Cangene explained that every shipment is monitored with temperature probes, and if there is an excursion below , both product integrity and container integrity would be assessed including the potential for additional container closure integrity testing studies to be executed under those specific conditions.

20. In addition to the simulated shipping, you presented actual shipping to the . You stated that following arrival at destination the container was held by the purchaser for an additional before opening the container and stopping the data loggers to further support a total shipment time of . During the 18 Aug 2014 telecon, we discussed that the actual shipping performed does not support a s summer shipping conditions, as the product was stored in the freezer for , and you agreed that this is the case. However this issue was not addressed in your response to the 04 Sep 2014 IR (amendment 125562/0/2), and you did not propose additional studies to support the shipping time. Please explain and provide supportive information.

Cangene stated that the protocol was implemented concurrently with an actual shipment of BAT. Once delivered to the purchaser, they placed it in a freezer before opening the container and stopping the data loggers. The freezer temperature at the destination was not communicated to Cangene but the storage in the freezer once the arrived at its destination kept the dataloggers within the acceptable range of -15°C to .

Cangene stated that the was qualified during the operational qualification of the shipping container; VAL_PQ_2260. The OQ utilized temperature chambers, acceptable industry practice, to simulate the conditions which could be expected to be seen during a worst-case condition of a summer shipment for the frozen product. They added that the design of the PQ_2260 study identified that an overseas shipment from the Cangene Winnipeg facility is typically , and that the targeted duration for the operational testing would be , which is longer than the predicted transport time. The study design also implemented a hold for the last transport leg as a challenge for shipment of frozen drug product.

They concluded that results of the simulation study confirmed that the pack-out procedure and shipping container were qualified, meeting the criterion of maintaining the temperature of

Cangene added that future air shipments using this container will be documented under a qualification report, with reference to PQ_2286, to further support that the procedure is controlled and reproducible.